

Solubilized Sertraline CompositionsField of the Invention

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This invention relates to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and a solubilizing agent which prevents gel formation or otherwise maintains the solubility of sertraline in a use environment containing chloride ions. The invention further relates to a method of treating a psychiatric or other illness comprising administering sertraline in such a solubilized composition to a mammal, including a human patient, in need of such treatment.

Background of the Invention

- 10 Sertraline is a selective serotonin reuptake inhibitor (SSRI), which is useful as an antidepressant and anorectic agent, and in the treatment of obsessive-compulsive disorder, premenstrual dysphoric disorder, post-traumatic stress disorder, chemical dependencies, anxiety-related disorders, panic and premature ejaculation.
- 15 Sertraline is most commonly prescribed for therapy of depressive illness, in the general dose range 50-200 mg/day. Sertraline has an elimination half-life of 23 hr and is dosed once daily. Commercially, sertraline is available as the hydrochloride salt which is undeniably therapeutically effective, many patients having availed themselves of the benefits of this drug.
- 20 Some forms of sertraline, particularly salts which exhibit high solubility, can be problematic, however. Such salts, generally those having an aqueous solubility in excess of 10 mg/mL, can exhibit a tendency to form a gel and/or exhibit reduced solubility (e.g., precipitate as a salt or as the free base having a lower solubility in the environment of use than the salt form originally administered) when exposed to a use
- 25 environment containing chloride ions such as the gastrointestinal tract. The gel itself tends to dissolve slowly and otherwise releases sertraline at a slow rate, thereby affecting absorption. It is not known whether gelation is the only mechanism which impacts the solubility of sertraline in a use environment. However, therapeutic difficulties can accordingly arise from administering an immediate-release dosage
- 30 form *in vivo* if solubility is affected, regardless of mechanism. Problems can similarly arise in the case of controlled-release dosage forms since the controlled release profile of the dosage form can be altered *in vivo* by factors affecting solubility. The

unanticipated phenomenon of gelation of sertraline salts in a chloride ion-containing environment can thus create therapeutic difficulties by unexpectedly altering the release profile of a dosage form, whether immediate-release or controlled-release. The mechanism of sertraline gelation is not well understood, and can be all the more
5 problematic therapeutically since the release characteristics of a gel formed *in situ* may not be anticipated.

In particular, gelling of sertraline in sustained-release dosage forms can be detrimental in those sustained release systems known as non-eroding matrix systems, reservoir systems, and osmotic systems. In each of these types of
10 sustained release formulations release of the drug is dependent on transport of the drug across a distance within the device (matrix or coating layer) to the surrounding fluid. This drug transport can occur by diffusive or convective mechanisms. In both mechanisms, formation of a gel can reduce transport by an order of magnitude or more and in some cases can result in devices that exhibit incomplete drug release
15 (e.g., less than 70% of the total drug in the formulation).

Summary Of The Invention

This invention provides a composition of matter, suitable for administration to a mammal, including a human, comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of an excipient, herein termed a "solubilizing
20 agent" sufficient to effect a concentration of dissolved sertraline in a use environment containing chloride ions which is at least 1.5 times higher, preferably 2 times higher, more preferably 3 times higher than the concentration effected by a comparative composition of matter (i.e., a control) identical thereto but for the inclusion of said solubilizing agent. The use environments mainly intended are the aqueous *in vivo*
25 digestive fluids of the gastrointestinal (GI) tract including the stomach, small intestine and large intestine, and aqueous *in vitro* chloride ion-containing test media, as further described below. The compositions are suitable for formulating into oral dosage forms including tablets, capsules, multiparticulates, powders for oral suspension, and unit dose packets (sometimes referred to in the art as a "sachet"). In addition the
30 compositions can be used in liquid dosage forms such as oral solutions or suspensions and injectable formulations. For making the compositions of this invention into oral dosage forms, conventional techniques known to the art can be

employed. The composition can additionally comprise other conventional pharmaceutical ingredients and/or a pharmaceutically acceptable carrier.

By this invention, it has been determined that in cases of dosage forms containing sertraline salts which form gels or which otherwise exhibit reduced solubility in a use environment, solubility may advantageously be increased, and in some cases solution viscosity may be advantageously decreased, by employing the sertraline salt together with a solubilizing agent which increases the sertraline's solubility. The solubilizing agent preferably also maintains solubility, meaning that the level of dissolved sertraline in a use environment, regardless of the salt employed, is held at a concentration greater than or equal to 1.5 times the concentration of sertraline in a like formulation without solubilizing excipient, for at least 2 hours. For many dosage forms it may be advantageous to maintain the sertraline concentration greater than or equal to 1.5 times the concentration of sertraline in like formulations without solubilizing excipient for longer periods of time such as 4 hours, 8 hours, 16 hours, or 20 hours, and this can be effected by the choice and amount of solubilizing agent. It has otherwise been determined that in a chloride ion-containing use environment without a solubilizing agent, for example a test environment such as 0.075M sodium chloride solution, sertraline solubility is generally less than 10 mgA/mL, usually less than 5 mgA/mL, regardless of the salt employed, and despite the fact that many of the salts themselves exhibit solubilities in pure water (i.e., no chloride ions) well in excess of 10 mgA/mL. Solubilizing agents thus could also be construed to be compounds that maintain sertraline concentrations of 10mgA/ml or greater in chloride-ion-containing environments of use.

Reference herein to "a solubilizing agent" herein, including the claims, shall be understood as also including the use of more than one solubilizing agent in a composition, added separately or as a mixture.

As mentioned above, the term "use environment" can refer to the aqueous *in vivo* chloride ion-containing digestive fluids of the stomach, or to an *in vitro* chloride ion-containing aqueous environment used to test a dosage form for its sertraline release characteristics. A useful *in vitro* test environment for purposes of this invention is 0.075M sodium chloride. 0.075M sodium chloride is preferred as a test medium because of its ready availability and similar chloride ion concentration to the

lower levels of chloride ions found in the fluids in the GI tract. Blood & Other Body Fluids, Dorothy S. Dittmer, ed., Federation of American Societies for Experimental Biology, Washington, D.C., 1961, pp. 404-419. Thus, as an additional feature, this invention provides an *in vitro* test to determine whether a dosage form is within the

5 scope of the invention. That is, the invention provides a composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce and to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline which is at least 1.5 times higher than the concentration effected by a comparative composition of matter

10 identical thereto but for the inclusion of said solubilizing agent. Agitation should be employed during the test although, as explained below, the degree or type of agitation is not critical. Salt solution temperature is not believed to be particularly critical so long as it is about 37°C, plus or minus 3°C, throughout the test. Excipients, including the solubilizing agent(s) should be at the desired concentration in the

15 aqueous test solution prior to adding sertraline and sodium chloride. Sertraline is then added to a concentration ranging between 80% to 100% of its saturation concentration in the test solution. This solution should be decanted off or filtered away from any solids. To this solution a 3M NaCl solution is slowly added with stirring until the NaCl concentration in the test solution is 0.075M. The sertraline

20 concentration in this test solution after 2 hours is compared with a control solution made in the same manner and consisting of the same components except the solubilizing agent.

Alternatively, a solubilizing excipient can be identified in an *in vivo* test such as a crossover study. In an *in vivo* crossover study a solubilized sertraline-

25 containing dosage form is dosed to half a group of 12 or more humans and, after an appropriate washout period (e.g., one week) the same subjects are dosed with a dosage form otherwise identical but for inclusion of the solubilizing agent. The other half of the group is dosed with the non-solubilized dosage form first, followed by the solubilized dosage form. Maximum concentration in the blood (C_{max}) and/or

30 bioavailability, measured as the area under the curve (AUC) for a plot of the concentration of sertraline in blood versus time, is determined for each group. By comparison, assessment of the solubilized dosage form can be made. If the average


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C_{\max} or AUC for the formulation containing the solubilizing agent is greater by 10% or more than the formulation without the solubilizing agent, then the solubilizing excipient is an embodiment of this invention. It is preferred that the C_{\max} and/or AUC be greater by at least 15%, and more preferred either or both be greater by at least 20%. The determination of AUC's is a well known procedure and is described, for example, in "Pharmacokinetics; Processes and Mathematics," by Peter Welling (ACS Monograph 185, Amer. Chem. Soc., Wash. D. C., 1986). Thus, as an additional feature of the invention, the invention provides a composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to effect, *in vivo*, a C_{\max} and/or an AUC which is greater by at least 10% than the C_{\max} and/or AUC effected by a comparison composition of matter (i.e., a control) identical thereto but for the inclusion of said solubilizing agent.

The invention further provides a method of increasing the solubility of sertraline in an aqueous chloride ion-containing environment, comprising administering said sertraline in a composition of matter comprising sertraline and a solubilizing agent.

The invention is surprising in that, prior to the invention, it was not known that (1) the phenomenon of reduced sertraline solubility in chloride ion-containing environments existed, nor that (2) any chemical agent existed which would reduce or prevent sertraline gelation or reduced sertraline solubility in chloride ion-containing use environments or otherwise operate to increase sertraline's solubility in such use environments. The term "solubilized sertraline" is used herein to refer to a composition comprising sertraline or a sertraline salt plus an excipient (i.e. the solubilizing agent) which prevents gelation or otherwise increases, and preferably maintains, the solubility of the sertraline salt in an *in vivo* or *in vitro* chloride ion-containing use environment. Likewise, the term "solubilize" is used to denote that the solubility of a sertraline salt is being increased by at least 1.5 times in a use environment over what it would be in the absence of a solubilizing agent.

The invention is preferred for use with the aspartate, acetate, and lactate salts which are salts that exhibit high solubilities in water relative to the free base. These salts are disclosed in commonly assigned co-pending application PC9337JTJ, filed



as a PCT application designating the United States, and herein incorporated by reference.

For convenience and consistency, reference to "sertraline" in terms of therapeutic amounts herein, including the claims, is to active sertraline, abbreviated herein as "mgA", i.e., the non-salt, non-hydrated free base having a molecular weight of 306.2. Amounts in mgA can conveniently be converted to equivalent weights for whatever salt form is desired.

Many solubilizing agents useful herein can be grouped into several broad categories:

1. Organic acids and organic acid salts;
2. Partial Glycerides, i.e., less than fully esterified derivatives of glycerin, including monoglycerides and diglycerides;
3. Glycerides;
4. Glyceride derivatives;
5. Polyethylene glycol esters;
6. Polypropylene glycol esters;
7. Polyhydric alcohol esters;
8. Polyoxyethylene ethers;
9. Sorbitan esters; and
10. Poxoxyethylene sorbitan esters.
11. Carbonate salts

Detailed Description

The amount of solubilizing agent employed in a composition according to the invention depends on the particular solubilizing agent employed.

In the case of solubilizing agents which are organic acids the preferred amount of solubilizer can be calculated as a ratio multiplied by the quantity of sertraline to be used, wherein the ratio is of organic acid solubility to solubility of sertraline salt:

(organic acid or salt solubility/sertraline or sertraline salt solubility) x quantity of sertraline

where the solubilities referred to are in mg/ml. The above expression is approximate, and some adjustment may be advantageous for optimization. Generally the above expression will give a quantity which is plus or minus 25% of the final value employed, although higher quantities of solubilizing agent can be incorporated without any particular additional advantage. In addition, organic acid salts can be added to modify the pH and/or solubility of the organic acid, effectively optimizing the solubilization effect of the agents.

For other types of solubilizing agents listed, typically the amount of solubilizing agent employed in the dosage form will be 1 to 150% by weight of the amount of sertraline employed therein, preferably 1 to 100%, more preferably 3 to 75%. Amounts of solubilizing agent higher than 150% may be employed, although it is believed that in most cases no particular advantage would be provided.

Salts of sertraline or excipients that in combination with sertraline aid in solubilizing sertraline can be beneficial to virtually any type of sertraline dosage forms intended for oral administration, including immediate release as well as controlled release systems, including (1) sustained-release dosage forms which meter out sertraline as they progress through the gastrointestinal system and (2) delayed release systems which release sertraline after an initial delay period following ingestion. Immediate-release systems are well known and commercially available in both solid and liquid formulations. Controlled release dosage forms of sertraline are discussed and disclosed in commonly assigned co-pending applications Pfizer Docket PC9337JTJ and PC9824JTJ, each of which is a PCT application designating the United States and each herein incorporated by reference in its entirety.

Solubilized sertraline can enhance release from the dosage form by increasing the concentration gradient for diffusive based systems such as matrix dosage forms and reservoir dosage forms. Solubilized sertraline can also enhance delivery from osmotic dosage forms in that a more soluble sertraline can increase the osmotic pressure in the core and increase the sertraline concentration in the fluid that is pumped or extruded out of the dosage form. In addition, solubilized sertraline can benefit sustained-release formulations by aiding absorption of drug from the G.I.

Examples of compounds within the other categories mentioned above are summarized in Table 1.

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2812 2813 2814 2815 2816 2817 2

Table 1**Solubilizing Agents**

Class	Examples, Chemical Name	Examples, Trade Designation, (Vendor)
Partial Glycerides	Glyceryl Monocaprylate	Monocaprylin [®] (Sigma), Capmul [®] MCM(Abitec), Imwitor [®] 308 (Hüls)
	C8-C10 Partial Glycerides	Capmul [®] MCM (Abitec), Imwitor [®] 742 (Hüls), Imwitor [®] 988 (Hüls)
	Glyceryl Monooleate	Myverol [®] 18-99 (Eastman), Calgene [®] GMO (Calgene), Capmul [®] GMO(Abitec)
	Glyceryl Monolinoleate	Myverol [®] 18-92 (Eastman)
	Glyceryl Monostearate	Imwitor [®] 191 (Hüls) Calgene [®] GSO(Calgene)
	Glycery Monolaurate	Imwitor [®] 312 (Hüls) Calgene [®] GLO (Calgene)
	Glyceryl Dilaurate	Capmul [®] GDL (Abitec)
Glycerides	Triacetin	Triacetin (Sigma)
Glyceride Derivatives	PEG-Derivitized Glycerides	Cremophor [®] RH40, Cremophor [®] RH60 (BASF), Acconon CA5, CA-9, CA-15, W230, TGH (Abitec)
	Polyglycolized Glycerides	Gelucire [®] 44/14, 42/12, 50/13, 53/10, 35/10, 48/09, 46/07, 62/05, 50/02; Labrasol [®] (Gattefosse); Capmul [®] 3GO; 3GS, 6G2O, 6G2S, 10G4O, 10G100 (Abitec)
Polyethylene glycol Esters	PEG 200 Monolaurate, PEG 400 Monolaurate, PEG 600 Monolaurate	Calgene [®] 20-L, Calgene [®] 40-L, Calgene [®] 60-L
	PEG 200 Monostearate, PEG 400 Monostearate, PEG 600 Monostearate	Calgene [®] 20-S, Calgene [®] 40-S, Calgene [®] 60-S
	PEG 200 Dilaurate, PEG 400 Dilaurate, PEG 600 Dilaurate	Calgene [®] 22-L, Calgene [®] 42-L, Calgene [®] 62-L
Polypropylene Glycol Esters	Propylene Glycol Dicaprylate	Captex [®] 200 (Abitec)
Polyhydric Alcohol Esters	Diethylene Glycol Monolaurate	Calgene [®] DGL

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	Propylene Glycol Monolaurate	Calgene [®] PGML
	Ascorbyl Palmitate	Ascorbyl Palmitate (Sigma)
Polyoxyethylene Ethers	PEG Lauryl Ether	Nonionic L-4 (Calgene)
	PEG Stearyl Ether	Nonionic S-20 (Calgene), Myrj 45, 52, 53, 59 (Sigma)
Sorbitan Esters	Sorbitan Monolaurate	Calgene [®] SML, Span [®] 20 (Sigma)
	Sorbitan Monooleate	Calgene [®] SMO, Span [®] 80 (Sigma)
Polyoxyethylene Sorbitan Esters	POE-20 Sorbitan Monolaurate	Calgene [®] PSML-20, Span [®] 20(Sigma), Tween 20 (Sigma), Capmul [®] POE-L (Abitec)
	POE-20 Monooleate	Tween [®] 80, PSMO-20
Saccharide Esters	Sucrose Monolaurate	Ryoto LW-1540 (Chem Service)
Phospholipids	Phosphatidyl choline	Lecithin (Sigma)
	Mixed phospholipids	Emphos D70-30C (Witco)
Block Co-polymers	PEO-PPO Block Copolymers	Pluronic [®] F-68, F127, L-62 (BASF)
Polyethylene Glycols	PEG 3350	Various sources

- In addition other compounds useful as solubilizing agents in the invention are ethyl propionate, methyl paraben, propyl paraben, propyl gallate, niacinamide, ethyl vanillin, paraaminobenzoic acid, butylated hydroxyanisole, imidurea, and glycine. It is also noted that preferred compositions include mixtures of an organic acid with or without a corresponding organic acid salt, and one or more of the non-organic solubilizers listed above or in Table 1. It is also noted that it has generally been observed that in order to be most effective the solubilizer should have a solubility in the aqueous chloride-ion containing use environment of at least 1mg/ml, and preferably greater than 5mg/ml.

A preferred group of solubilizing agents, in addition to the preferred organic acids previously mentioned, includes those in Table 2.

Table 2**Preferred Solubilizing Agents**

Class	Examples, Chemical Name	Examples, Trade Names (source)
Partial Glycerides	Glyceryl monocaprylate	Monocaprylin [®] (sigma), Capmul [®] MCM(Abitec), Imwitor [®] 308 (Hüls)
	C8-C10 Partial Glycerides	Capmul [®] MCM (Abitec), Imwitor [®] 742 (Hüls), Imwitor [®] 988 (Hüls)
	Glyceryl Monostearate	Imwitor [®] 191 (Hüls) Calgene [®] GSO(Calgene)
	Glyceryl Monolaurate	Imwitor [®] 312 (Hüls) Calgene [®] GLO (Calgene)
Glycerides	Triacetin	Triacetin [®] (Sigma)
Sorbitan Esters	Sorbitan Monolaurate	Calgene [®] SML, Span [®] 20 (Sigma)
	Sorbitan Monooleate	Calgene [®] SMO, Span [®] 80 (Sigma)
Phospholipids	Phosphatidyl choline	Lecithin [®] (Sigma)
	Mixed phospholipids	Emphos D70-30C (Witco)
Block Co-polymers	PEO-PPO Block Copolymers	Pluronic [®] F-68, F127, L-62 (BASF)
Polyethylene Glycols	PEG 3350	Various sources

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Note: Commercial vendors shown above are as follows:

Abitec Corp. Janesville, WI

BASF, Parsippany, NJ

Calgene Chemical Inc. Skokie, IL

10 Chem Service, Inc., West Chester, PA

Hüls America, Piscataway, NJ

Sigma, St. Louis, MO

Witco, Houston, TX

Preferred combinations of solubilizing agents include (1) an organic acid plus a salt of the same or a different organic acid, (2) an organic acid plus a non-ionic solubilizing agent such as any of those listed in Table 1, and (3) an organic acid plus a salt of the same or a different organic acid plus a non-ionic solubilizing agent.

- 5 Particularly preferred individual solubilizing agents include aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, glutamic acid, and calcium carbonate. Aspartic acid, glyceryl monocaprylate, glyceryl monolaurate and calcium acetate are most preferred.

- As previously discussed, a dosage form can be tested *in vitro* to determine
10 whether an excipient has a solubilizing effect on sertraline in a chloride-ion containing use environment and thus is useful as a solubilizing agent. A 0.075M NaCl solution is preferred for use as a test medium although other chloride-ion containing solutions with equivalent or higher chloride ion concentration than 0.075M (e.g., 0.1N HCl or isotonic saline) may be used to determine the solubilizing effect of a test excipient. In
15 some cases reduced solubility is evident simply by adding a dosage form such as a powder to the test medium because gelation is visible. Similar problems may be evident in a dosage form such as a tablet if the tablet is, for example, cut open and gelation is visible on its open face. A recommended procedure is to initially make a solution containing the desired excipients, including solubilizing agent(s). The
20 excipients can be at any concentration relevant to the intended dosage form, but are typically for organic acids and soluble salts or sugars 80-100% of saturation. For other surfactant-like compounds, concentrations typically range from 1 to 150% of the sertraline concentration in the test solution. Sertraline is added to this excipient-containing solution at a concentration typically 80-100% of saturation. The solution is
25 filtered or decanted to remove any solids and then a 3M solution of sodium chloride is added until the sodium chloride concentration is 0.075M. The concentrated sodium chloride solution should be added dropwise with stirring. This test medium should be kept at a temperature on the order of 37°C for at least 2 hours at which time the sertraline concentration in solution is determined. It is preferred that the sertraline
30 concentration be maintained for 4 hours, more preferably for 8 hours, still more preferably for 16 hours, and most preferably for at least 20 hours. The amount of agitation is not critical. When sampling the test medium, filtration or centrifugation

can be employed to obtain solution that is free of any solids or gel material, and also to avoid inclusion of particulates (which may contain sertraline) in the sample.

Analysis of the samples to determine sertraline concentration can be accomplished via several conventional analytical methods, such as by high performance liquid

- 5 chromatography (HPLC). For example, sertraline concentrations can be determined using reverse phase HPLC with a ULTRACARB® 5 ODS 4.6 x 250 mm column (Phenomonex, Torrance, CA), and a mixture of acetic acid, triethylamine, acetonitrile, and water as mobile phase, with UV detection at 230 nm. For example, the mobile phase can be prepared by combining, with stirring, 2.86 ml of glacial acetic acid, 3.48
10 ml of triethylamine, diluting to a liter with water, and filtering and degassing. Flow rates are typically on the order of 1.5 ml/min, and retention times about 4 minutes.

- Dosage forms with solubilizing agent can be formulated by conventional techniques. Immediate release dosage forms can be capsules, tablets, multiparticulates, liquid solutions or suspensions. Capsule formulations can be either soft
15 gelatin capsules where the sertraline is either dissolved or suspended within the capsule core or hard gelatin capsules filled with multiparticulates, tablets or a liquid (solution or suspension) fill. Immediate release tablets can be by techniques standard in the industry by simply including the solubilizing agent as one or more of the tablet excipients. Likewise immediate-release multiparticulates can be made that
20 include solubilizing agents by techniques such as extension spheronization, rotary granulation, coating seed cores or other methods common in the pharmaceutical industry. Liquid formulations consisting of a solution or suspension or both can be made by methods common in the pharmaceutical industry.

- Controlled-release dosage forms can also be made that include solubilizing
25 agents by methods common in the pharmaceutical industry. Controlled release dosage forms include a wide variety of dosage forms that impart control over the dissolution rate or rate of release of sertraline from the dosage form. Such dosage forms include but are not limited to sustained release, delayed and then immediate release, delayed and then sustained release and a dosage form with a small portion
30 of sertraline released immediately and then followed by the majority of the sertraline in the dosage release at a sustained rate. Other algorithms of release can also be

attained such as pulsatile release. Many such formulations are described in
aforementioned co-pending applications PC9337JTJ and PC9824JTJ.

Standard techniques can be used to make controlled release dosage forms.
For example, tablets can be made by commonly used direct compression methods
5 that contain sertraline and a solubilizing agent. To provide delayed release, a pH-
sensitive coating can be applied to these tablets via a side-vented pan coater (e.g.,
HCT-60 tablet coater, Vector Corp.). The pH sensitive coating is resistant to low pH
environments such as typically in the stomach and then dissolves, releasing
sertraline, in neutral pH environment such as typically in the small intestine. Such
10 coating materials (e.g., cellulose acetate phthalate or methacrylic acid copolymer) are
common in the pharmaceutical industry. Alternatively, the tablets can be coated with
a porous or semipermeable membrane coating to provide sustained release of the
tablet cores. A particularly useful process for applying a membrane coating
comprises dissolving the coating polymer in a mixture of solvents chosen such that
15 as the coating dries, a phase inversion takes place in the applied coating solution,
resulting in a membrane with a porous structure. Numerous examples of this type of
coating system are given in European Patent Specification 0 357 369 B1, published
March 7, 1990, herein incorporated by reference. Many other types of controlled
release dosage forms can also be made that benefit from the inclusion of solubilizing
20 agents such as matrix systems which include but are not limited to 1) non-eroding
matrices, tablets, multiparticulates and hydrogel-based systems; 2) hydrophilic
eroding, dispersible or dissolvable matrix systems, tablets and multiparticulates; and
3) coated matrix systems. Another class of controlled-release dosage forms consists
of reservoir systems where release of the drug is modulated by a membrane, such as
25 capsules and coated tablets or multiparticulates. A third class consists of osmotic-
based systems such as 1) coated bilayer tablets; 2) coated homogeneous tablet
cores; 3) coated multiparticulates; and 4) osmotic capsules. A fourth class consists
of swellable systems where drug is release by a swelling and then extrusion of the
core components out through a passageway in a coating or surrounding shell or
30 outer layer.

The invention is further illustrated by the following examples, which are not to
be taken as limiting.

Example 1

This example illustrates that organic acids have the ability to raise the solubility of the hydrochloride salt of sertraline. The acids were tested by dissolving the candidate acid in water and then stirring excess sertraline hydrochloride in the acid solution for at least 8 hours. The concentration of sertraline in the supernatant was then measured by HPLC analysis. The results of this test are shown in Table 1-1, below. Most of the acids listed in the table successfully raised the solubility of sertraline hydrochloride (normal solubility 2.5 mg/ml).

Table 1-1

Excipient	Approximate Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
D,L-malic acid	900	21
Citric acid	600	20
Erythorbic acid	400	19
Adipic acid	14	12
Maleic acid	700	6.4
L-aspartic acid	10	5.5
Tartaric acid	1400	5.5
L-glutamic acid	12	5.4
Fumaric acid	11	3.1
Tannic acid	2000	2.8
D,L-tyrosine	600	2.2

Preferred acids, based on the above-described test, are malic, citric, erythorbic, and adipic acids. Maleic, L-aspartic, tartaric, and L-glutamic acids also significantly improved sertraline hydrochloride solubility. Some controlled-release dosage forms with such acids in the core will perform better than those without such acids. This is particularly true for osmotic-based formulations that deliver a solution of drug.

Example 2

This example illustrates that organic acids have the ability to raise the solubility of the acetate salt of sertraline by a test method similar to that used for the hydrochloride salt described in Example 1. The solubilizing agent, its concentration, and resulting sertraline solubility are shown in Table 2-1 below. Based on these results, preferred acids to include in a dosage form where increased sertraline

acetate solubility is desired are ascorbic, erythorbic, citric, lactic, aspartic, glutamic, and aconitic acids.

Table 2-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
Ascorbic acid	400	>425
Erythorbic acid	400	>330
Citric acid	600	146
Lactic acid	213	>294
Aspartic acid	7	110
Glutamic acid	12	108
Aconitic acid	500	>92
Itaconic acid	150	72
Succinic acid	77	28
None	--	64

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Example 3

10 This example illustrates that organic acids and three calcium salts have the ability to raise the aqueous solubility of the lactate salt of sertraline using a method similar to that used for the hydrochloride salt described in Example 1. The solubilizing agent, its concentration in the aqueous test solution, and the sertraline lactate solubility in the test solution are listed in Table 3-1 below. Solubility of sertraline lactate in water is approximately 125 mg/ml. The data below show that

15 eight organic acids effected sertraline lactate solubilities about the same as or higher than 125 mg/ml; adipic, erythorbic, itaconic, citric, aspartic, glutamic, histidine, and ascorbic. Also, a solution of a mixture of two of these acids also had high solubility; ascorbic and aspartic. Sertraline lactate solubility was also high in calcium salt solutions, either alone (calcium citrate) or mixed with ascorbic acid.

Tabl 3-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Lactate Solubility (mg/ml)
Adipic acid	14	360
Erythorbic acid	400	>217
Itaconic acid	150	>202
Citric acid	600	162
Aspartic acid	7	>155
Glutamic acid	12	>125
Histidine	42	>116
Ascorbic/Aspartic	400/7	116
Ascorbic	400	102
Glycine	250	66
Aconitic acid	200	<59
Tartaric acid	1400	12
Fumaric acid	11	<9
Sorbic acid	3	<9
Calcium lactate/ Ascorbic acid	50/400	160
Calcium citrate	10	165
Calcium carbonate/ Ascorbic acid	50/400	176
None	—	125

Example 4

- 5 The lower solubility of the sertraline chloride salt and of all sertraline lactate and sertraline acetate salts in the presence of high chloride concentrations suggest that core formulations are preferred for which sertraline stays in solution that is, it does not precipitate or form a gel-like material when chloride is present. Certain organic acids and salts were found to inhibit precipitation or gelation of sertraline when
- 10 chloride is present via the following screening test. Sertraline lactate was dissolved in water either alone (as a control) or with a candidate solubilizing agent. Sodium chloride was then added (as a concentrated solution) and the result observed. An excipient was considered beneficial if the solution remained clear and fluid. The more chloride that could be added to an excipient solution with the solution remaining
- 15 clear, the more beneficial was the excipient. Table 4-1 below shows the results of this screening test, indicating that all the excipients tested increased sertraline concentration in the chloride solutions.

Содержание

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Organic compounds (solubilizers) were screened for their ability to enhance the solubility of sertraline lactate in aqueous solutions with or without the presence of chloride. Excess sertraline lactate was added to an aqueous solution of the candidate solubilizer and, in most cases an organic acid. The organic acids were saturated in these solutions and the additional solubilizing agents were at the concentration shown in Table 5-1. The equilibrium sertraline solubility was measured. Then, sodium chloride was added to the saturated solution and the final sertraline concentration was measured. The results of these screening tests are summarized in Table 5-1.

Table 5-1

	Solubilizer	Solubilizer Concentration (mg/ml)	Organic Acid	Sertraline Solubility (mg/ml)	NaCl Concentration (mM)	Sertraline Concentration with NaCl (mg/ml)
1	None (control)	--	none	125	150	5
2	Monocaprylin	10	ascorbic	160	150	160
3	Triacetin	100	ascorbic	170	150	170
4	Monobutyrin	50	none	120	150	120
5	Diacetin	50	ascorbic	120	150	120
6	Imwitor [®] 312	10	ascorbic	120	150	120
7	Imwitor [®] 375	10	ascorbic	120	150	120
8	Imwitor [®] 742	50	none	120	150	120
9	Imwitor [®] 988	50	none	140	100	140
10	Triethyl citrate	50	ascorbic	160	150	160
11	Pluronic [®] L31	50	none	120	100	120
12	Cremophore [®] EL	50	ascorbic	120	150	120
13	Sucrose acetate isobutyrate	50	ascorbic	120*	150	120
14	Sodium capryl lactate	50	ascorbic	120	150	120
15	Sucrose monolaurate	50	none	150	150	150
16	Sodium lauryl lactate	50	ascorbic	120	150	120
17	Span 80	50	ascorbic	120	150	120

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Example 6

- This example illustrates that solubilizers for sertraline also can increase the rate of dissolution of sertraline. The effect of a candidate excipient on sertraline
- 5 dissolution rate was determined by adding solid drug, the candidate solubilizing excipient, and, in some cases, other excipients such as an organic acid and an osmagent (such as a sugar) to a 1.8 ml centrifuge tube. The sample tubes were spun at 14K G for 5 minutes in a microcentrifuge to pack the powder. 150 μ l gastric
- 10 buffer was added to the packed powder and the samples were gently agitated, then spun at 14K G in a microcentrifuge for 2 minutes. The samples were then removed from the microcentrifuge and allowed to stand undisturbed until the solution was removed. The solution was removed from the samples after a total of 10 minutes after gastric buffer was added to the powder pack, and analyzed by HPLC to determine the sertraline concentration.
- 15 The dissolution rate (mg sertraline/ml-min) was calculated from the measured concentration of dissolved sertraline in the supernatant as a function of time over the first 10 minutes of dissolution. These dissolution rates and the excipient mixtures for which they were measured are summarized in Table 6-1 below. As shown, several excipient mixtures containing solubilizers significantly (about 3X or greater) increased
- 20 the dissolution rate of sertraline, compared with sertraline alone and compared with sertraline and ascorbic acid.

Table 6-1

Candidate Excipient		Organic Acid	Organic Acid Conc. (wt%)	Osmagent	Osmagent Conc. (wt%)	Other Excipient	Other Excipient Conc. (wt%)	Sertraline Salt Form Conc. (wt%)	Sertraline Dissolution Rate (mg/ml-min)
Name	Concentration (wt%)								
None	--	none	--	none	--	none	--	lactate 100	
None	--	ascorbic	51.0	lactose	20	none	--	lactate 14	3.5
Imwitor [®] 312	5.0	ascorbic	49.5	lactose	12.5	CaCO ₃	5	lactate 14	20.9
Lecithin	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	10
PEG 3550	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.3
Capmul [®] MCM	5.0	ascorbic	71.0	none	--	none	--	lactate 24	14.5
Capmul [®] MCM	4.7	none	none	lactose	17	CaCO ₃ Ca citrate	4.7 47	lactate 13.1	4.3
Imwitor [®] 191	5.0	ascorbic	49.5	lactose	12.5	CaCO ₃	1.0	lactate 14	8.0
Myvrerol [®] (18-99)	5.0	ascorbic	49.5	lactose	12.5	none	--	lactate 14	6.4
Span [®] 60	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.5
Ascorbyl palmitate	6.8	none	none	lactose	74.2	none	--	lactate 19	4.3

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Methyl paraben/ propyl paraben/ propyl gallate Imwitor [®] 312	0.5/0.5/1.0	ascorbic	50.0	lactose	17.5	none	--	lactate 14	11.5
	6.8	aspartic	7402	none	--	none	--	lactate 19	5.3

Example 7

This examples illustrates a method for making osmotic tablets comprising a tablet core containing sertraline with and without solubilizing agents surrounded by a semipermeable asymmetric membrane coating. In this example the benefit of incorporating solubilizers into a controlled-release formulation containing sertraline is demonstrated. Sertraline-hydrochloride was triturated by hand for 10 minutes with citric acid and microcrystalline cellulose (Avicel PH 102, FMC) using a 6 1/2 inch diameter mortar and pestle. Magnesium stearate was then blended in as a lubricant by stirring with a spatula for 60 seconds. The weight ratio of sertraline-hydrochloride to citric acid to microcrystalline cellulose to magnesium stearate was 8.5:63.8:23.7:4; with a total weight of 10 grams. The blended mixture was pressed into 470 mg tablets in a modified hydraulic jack (manufactured by Dayton) fitted with a pressure gauge and 3/8 inch concave punch under 2500 PSI pressure for 2 seconds. The dimensions of the resulting tablets were 3/8 inch in diameter and 1/4 inch thick. A semipermeable membrane coating (as described in U.S. Patent 5,612,059 was applied to these tablets using a LDCS-20 pan coater (Vector Corp.) at a spray rate of 20 grams per minute, an inlet temperature of 40°C and air flow of 40 cfm. The coating solution contained by weight 10% Cellulose acetate, (Eastman Chemical, CA398-10), 2.5% polyethylene glycol (BASF, PEG 3350), 15% water and 72.5% acetone. The coated tablets were dried 1 hour at 50°C before testing. After drying, the weight of applied coating material was 15.4% of the total weight. Additional osmotic delivery tablets were prepared by using essentially the same procedure for making the tablet cores and applying the asymmetric membrane coating to the cores described above. The composition of the cores and coating solution varied as shown in Table 7-1. Significant core compositional changes shown include: the sertraline salt form, the type and amount of solubilizer, and the type and amount of osmagent. The amount of binder (Avicel®) lubricant (magnesium stearate), and solubilizer were varied as necessary to obtain good tableting and wetting properties. These tablets all contained a sertraline dose of 50 mgA/tablet.

Table 7-1

Example No.	Core Composition												Coating Solution				
	Core Weight (mg)	Drug		Solubilizer Acid		Solubilizer		Osmogent		Avicel wt %	Mg St. wt %	Other	Polymer Type	Polymer wt %	PEG wt %	Water wt %	Coating Weight (dry wt %)
		Salt Form	Wt %	Type	Wt %	Type	Wt %	Type	Wt %								
7a	470	chloride	12	none		none		lactose	66	20	2	none	CA	10	2.5	15	15.4
7b	470	lactate	14	none		none		lactose	65.4	19.3	1.33	none	EC	6	4	8	1
7c	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca Acetate	CA	10	2.5	15	11
7d	470	lactate	14	glutamic	10	MC	5	sucrose	50	15	none	Ca lactate, Myrj	EC	6	4	10	10.1
7e	470	lactate	14	aspartic	11	lm	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	10.3
7f	470	lactate	14	glycine	25	lm	5	fructose	28.5	25	2.5	none	CA	10	2.5	15	15.9
7g	470	lactate	14	aspartic	11	lm	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	20
7h	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca acetate	CA	10	2.5	15	10

The rates of release of sertraline from these formulations were determined testing the tablets in a USP Apparatus #2 with paddle stirring speed set at 100 rpm. The receptor solution used in the dissolution apparatus was 0.13M acetate buffer at pH 4.0 with 0.075M sodium chloride kept at 37°C. Samples of the receptor solution were taken at the times shown in Table 7-2. Analysis of sertraline released was determined by reverse-phase high-performance liquid chromatography (RP HPLC).

The results of release-rate tests performed using these procedures are listed in Table 7-2. The first two formulations listed, 7a and 7b show low release rates and are included as comparison examples. Both these formulations contain a sertraline salt (hydrochloride or lactate) and only lactose as the osmagent and no solubilizing excipients. The remaining formulations (7c-7h) listed in Table 7-2 all contain one or more solubilizing excipients and all demonstrate significantly higher release rates of sertraline compared with the formulations that do not contain solubilizers.

Table 7-2

Tablets of Example No	Fraction of Drug Released (%) At Specified Time						
	0 Hr	1 Hr	2 Hr	4 Hr	8 Hr	12 Hr	20 Hr
7a	0	0	0	0	0	0	0
7b	0	0	1	2	—	10 (17 hr)	12
7c	0	6	15	35	62	76	78
7d	0	0	0	4	19	28	44
7e	0	8	19	37	60	73	83
7f	0	0.7	6	17	37	54	78
7g	0	0.4	4	13	31	41	53
7h	0	8	18	38	56	64	66